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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,141	07/24/2003	Srinivas G. Rao	CYPR 101	5413

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DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/628,141	RAO ET AL.	
	Examin r	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communicati n appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12 and 13* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed February 28, 2006, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Informalities

Claims 1-14 are currently pending and are the subject of this Office Action. Claim 11 is withdrawn from consideration as being drawn to non-elected subject matter.

Claim Objections

Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4 and 9-10 recite the limitation "the selective" in Line 1 of each respective claim. There is insufficient antecedent basis for this limitation in the claims.

Claim 10 recites the limitation "The method of claim 1 wherein the selective norepinephrine (NE)-serotonin (5-HT) reuptake inhibitor (NSRI) comprises at least two of..." in Lines 1 and 2 (emphasis added). There is insufficient antecedent basis for this limitation in the claim.

Independent Claim 1 carries the limitation of an effective amount of a dual norepinephrine serotonin reuptake inhibitor (NSRI) to alleviate or prevent at least one symptom of atypical depression. There is no indication in the base claim that the NSRI agent comprises more than one compound. As such, Examiner has interpreted Claim 1 to mean a single compound NSRI. Claim 10 lacks antecedent basis for the added limitation of "at least two of" because the claim on which it depends has been interpreted to only comprise one NSRI agent as suggested by the word "a" in Line 3 and the word "inhibitor" in Line 4 of Claim 1. Further support for the interpretation that Claim 1 is drawn to a single NSRI inhibitor is found in the Specification at Page 5, Lines 16-24, Page 11, Lines 6-9 as well as in Example 2, Pages 23-24.

Rewriting Claim 10 as an independent claim may overcome this rejection provided there is support in the Specification for such an amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mouzin *et al.* (U.S. Patent No. 4,478,836) in view of Moret *et al.* (1985) and Ruoff (1996).

The '836 patent discloses milnacipran, salts of milnacipran, and derivatives thereof for use in the treatment of depression (see especially Abstract).

Moret *et al.* disclose that milnacipran is a dual norepinephrine (NE) serotonin (5-HT) reuptake inhibitor (see especially Abstract), has a NE:5-HT reuptake inhibition ratio of 2:1 (Table 4, page 1215), and can be used to treat depression at a dose of 50 mg twice a day (page 1218, last paragraph).

Ruoff discloses that the neurotransmitters serotonin and norepinephrine have been implicated in both perception of pain and the pathogenesis of depression and that antidepressants have been shown to be effective in the treatment of a variety of chronic pain syndromes, including peripheral neuropathic pain, headache, migraine, facial pain, fibrosis, and rheumatic pain (page S27). The reference further states that, "Regardless of whether depression is secondary to the pain syndrome or is the primary condition, the mood disorder should be thoroughly assessed and treated pharmacologically" (page S28, "Treatment Approaches"). Ruoff further discloses that the antidepressant, venlafaxine, exerts its antidepressant activity through selective inhibition of norepinephrine and serotonin uptake (Page S30, "Venlafaxine").

As noted by the Applicants, the relationship between chronic pain and depression is complex and not entirely understood. However, the treatment of

depression secondary to pain is suggested by the reference to be the same as that for treatment of other types of depression. Ruoff states on Page S32, last paragraph that:

> *"Clinicians must carefully assess patients prior to initiating antidepressant therapy. However, once depression is diagnosed, treatment in the patient with chronic pain is no different than in patients without pain. Antidepressant therapy should be started early and in full doses."*

Clearly, this statement, and in fact the entire disclosure of Ruoff, provides ample motivation to combine the above references.

No unobviousness is seen in the present methods given the known use of milnacipran to treat depression. In addition, the prior art is clear with regard to the relationship between pain and depression; as Applicants have stated in their arguments, the relationship is complex and not entirely understood. However, it is the diagnosis of depression in patients having chronic pain that is complex. Once the diagnosis has been properly made, the treatment is, as suggested by Ruoff, no different than that used for depression without pain. In fact, at the time the invention was made, the prior art made no distinction in the treatment of depression and atypical depression secondary to pain.

Thus, Claims 1-7 and 12-13 would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art. This is especially true given that milnacipran was known in the art to be a dual norepinephrine serotonin uptake inhibitor useful in the treatment of depression due to its minimal side effects. The drug had been

used, in the doses instantly claimed, to treat major depression (Moret *et al.*, page 1218). Lastly, Ruoff explicitly states that the treatment of depression in a patient having chronic pain is no different than in patients without pain.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mouzin *et al.* (U.S. Patent No. 4,478,836) in view of Moret *et al.* (1985) and Ruoff (1996) as applied to claims 1-7 and 12-13 above, and further in view of Shuto *et al.* (J. Med. Chem., 1995, 38:2964-2968).

Mouzin, Moret, and Ruoff teach as above. Shuto *et al.* disclose that milnacipran, a clinically used antidepressant, is an effective NMDA receptor antagonist (Table 1, Page 2966). The ability of milnacipran, a dual serotonin norepinephrine inhibitor, to antagonize NMDA receptors is an inherent property of the drug as evidenced by Shuto *et al.* and is therefore rendered obvious by the combined references.

Thus, the method of Claim 8 would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mouzin *et al.* (U.S. Patent No. 4,478,836) in view of Moret *et al.* (1985) and Ruoff (1996) as applied to claims 1-7 and 12-13 above, and further in view of Puech *et al.* (Int. J. Psychopharm., 1997, 12:99-108).

Mouzin, Moret, and Ruoff teach as above. Puech *et al.* disclose that milnacipran, a new serotonin and noradrenaline (synonymous with norepinephrine) reuptake

inhibitor, has comparable or superior antidepressant effects to tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) without the side effects of TCAs (see especially Abstract). There have been no reported increases in seizures associated with milnacipran in the over 4000 patients who have received the drug in therapeutic trials (Page 104, "Tolerability and Safety"). Table V (page 105) of the reference compares the adverse events associated with milnacipran (50 mg twice a day), TCAs, and SSRIs.

Thus, the method of Claim 9 would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James D. Anderson
Examiner
Art Unit 1614

May 15, 2006

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER